Hepatic Encephalopathy Update: Reports from the 2013 American College of Gastroenterology Meeting

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The studies presented have not been validated by peer reviewers, but are platform presentations, posters, etc presented at a scientific meeting. Use caution in drawing conclusions until published in peer-reviewed journals.

Objectives:
After reading and studying this newsletter, the participant should be able to:

- Recognize the central role of aberrant nitrogen metabolism in the pathogenesis of hepatic encephalopathy
- Assess the results of selected studies relating to the burden and treatment of hepatic encephalopathy presented at the American College of Gastroenterology 2013 Annual Scientific Meeting and Postgraduate Course

Introduction
The complex neuropsychiatric syndrome referred to as hepatic encephalopathy (HE) is a debilitating and life-threatening consequence of liver disease. In fact, HE complicates up to 1 in 4 presentations of acute liver failure (ALF). The spectrum of clinical severity associated with HE is broad and can include subtle loss of cognitive functions, lethargy, depressed consciousness, and coma. Astonishingly, between 60% and 80% of patients with liver cirrhosis are estimated to suffer with a form of HE referred to as minimal hepatic encephalopathy (MHE), characterized by decreased attention, poor concentration, impaired memory, sleep disturbances, reduced speed of information processing and altered motor abilities. Aberrant nitrogen metabolism has been demonstrated to play a central role in the pathogenesis of HE; therefore, HE is considered to be a clinical manifestation of the low-grade cerebral edema associated with altered neuron-astrocyte crosstalk exacerbated by hyperammonemia and oxidative stress. These neural consequences are a result of dysregulation of the gut-liver axis in cirrhosis, complicated by portal hypertension, which allows ammonia to bypass the liver and enter the systemic circulation. This condition, referred to as portosystemic encephalopathy, results in ammonia uptake by astrocytes in the brain and subsequent conversion to glutamine, which exerts an osmotic effect and ultimately induces astrocytic swelling and brain edema. However, it should be noted that the relationship between ammonia and HE remains somewhat unclear. Although raised plasma ammonia levels are often observed in patients with acute-on-chronic liver failure, ALF, and in those with intracranial pressures >25 mm Hg, there is often a poor correlation between arterial plasma ammonia levels and the manifestation of HE in patients with cirrhosis. Additionally, the correlation between ammonia concentration and astrocyte swelling is unclear and may be modulated by a variety of factors.

This newsletter will review selected research related to HE reported at the American College of Gastroenterology 2013 Annual Scientific Meeting and Postgraduate Course, which took place in San Diego, California, on October 11-16, 2013.

Advances in the Understanding of the Burden of Hepatic Encephalopathy in Patients with Cirrhosis
Although it has long been known that cirrhosis is responsible for significant morbidity and healthcare costs in the US, there remains a paucity of data regarding the inpatient burden of complications of cirrhosis in the US. The poster...
presentation by Sethi et al described the results of an analysis of all subjects in the National Inpatient Sample Database for which the principal discharge diagnosis was a specific complication of cirrhosis, including HE, from 2005 through 2010.\textsuperscript{19} Study results from the 377,270 hospital admissions analyzed over the study period revealed that 56,032 inpatient discharges were attributed to complications of cirrhosis in 2005 and that the number increased significantly ($P<.05$) to 72,035 by 2010 (Figure 1).

Regarding study results specific to HE, the data indicated that 66.8% of discharges in 2010 were attributable to HE, the average total charges due to HE were $36,978, and the specific percent in-hospital mortality due to HE was 6.7%. The study authors concluded that inpatient admission rates and associated costs for complications of cirrhosis were on the rise and that further analyses would be required to identify the specific factors associated with these admissions in order to reverse this trend using targeted interventions. Additionally, the study authors noted that although hospital mortality as a result of complications of cirrhosis was high, it has been on the decline in recent years.

Basu and colleagues reported results of a study aimed at investigating the association of restless leg syndrome (RLS) and small intestinal bacterial overgrowth (SIBO) in HE among decompensated cirrhotics.\textsuperscript{20} To accomplish this aim, 108 patients were recruited and subdivided into three groups of 36 patients each. Those in Group A were decompensated cirrhotics, members of Group B had chronic liver disease without cirrhosis, and those in Group C served as healthy controls. In addition to undergoing sleep testing for RLS, patients in Groups A and B underwent neuropsychometric and flicker testing to determine if they had MHE or overt HE (OHE). Study results revealed that the largest number and percentage of patients with either RLS or SIBO or both were in Group A (Table 1).

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>RLS, n (%)</th>
<th>SIBO, n (%)</th>
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<tbody>
<tr>
<td>A: decompensated cirrhotic (36)</td>
<td>24 (67)</td>
<td>14 (39)</td>
</tr>
<tr>
<td>B: chronic liver disease without cirrhosis (36)</td>
<td>1 (3)</td>
<td>7 (19)</td>
</tr>
<tr>
<td>C: healthy controls (36)</td>
<td>2 (6)</td>
<td>3 (8)</td>
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</table>

Furthermore, of those in Group A, 16 of 20 (80%) had OHE and RLS and 8 of 16 (50%) had MHE and RLS. Additional study results revealed that serum ammonia had no impact on the presence or absence of RLS. The study authors concluded that decompensated cirrhotics with HE in this study had a high incidence of RLS with portal hypertension, but that larger trials would be necessary to validate their findings.

### Advances in the Treatment of Hepatic Encephalopathy

While it is known that the creation of a transjugular intrahepatic portosystemic shunt (TIPS) can effectively treat complications of portal hypertension, it is also clear that excessive shunting can cause life-threatening HE and necessitate revision of the TIPS.\textsuperscript{21} The limited data available regarding the success of this intervention was addressed in a poster presentation by Olaywi et al.\textsuperscript{19} They reported on a retrospective review study of 9 patients who underwent an elective TIPS placement for ascites and later required narrowing for refractory HE or hepatorenal syndrome with mild encephalopathy within a 3-year period.\textsuperscript{22} The underlying etiology of liver disease for the patients in the study is listed in Table 2.
Underlying etiology of liver disease | Number of patients
---|---
Non-alcoholic fatty liver disease | 3
Hepatitis C | 2
Alcoholic hepatitis | 2
Autoimmune hepatitis | 1
Primary biliary cirrhosis | 1

Table 2. Underlying etiology of liver disease in 9 patients identified from a retrospective review of all patients within a 3-year period who underwent an elective TIPS placement for ascites and later required narrowing for refractory HE or hepatorenal syndrome with mild encephalopathy. HE = hepatic encephalopathy; TIPS = transjugular intrahepatic portosystemic shunt.

Study results revealed that 11 TIPS revisions using a variety of techniques were performed on the 9 patients and that 9 of the 11 revisions were considered to have been successful based on improved hepatopedal flow and improvement in HE. Additionally, improvements in several important variables were associated with successful revisions. For example, hospital admissions for HE decreased from a mean of 3.7±1.8 admissions per patient pre-TIPS revision to 1.5±1.5 admissions post-TIPS revision. Furthermore, study data demonstrated that the length of stay per HE admission was 6.4±6.1 days pre-TIPS revision, but 4.4±3.2 days post-TIPS revision narrowing. The mean portosystemic gradient also improved as a result of revision, changing from 10.5±4 mm Hg after initial TIPS to 4.8±2.3 mm Hg after successful narrowing. Regarding complications, 3 of 9 patients went on to develop ascites following TIPS revision; however, this was easily managed with diuretics. The study authors concluded that TIPS narrowing was an effective means by which patients with HE secondary to TIPS placement could be managed without significantly inducing recurrence of ascites. They suggested that the use of an atrium on wall stent or a balloon expandable stent were effective techniques for TIPS revisions, although they noted that larger studies would be necessary to support this assertion.

A poster presentation by Wakim-Fleming et al reported on a study which tested the hypothesis that simvastatin may prevent the development of HE in patients with cirrhosis by improving nitric oxide (NO) production in the liver microcirculation and by decreasing hepatic resistance. To accomplish this goal, they used univariable analysis and multivariable logistic regression to analyze the medical records of 45 cirrhotic patients taking simvastatin and 46 cirrhotics not on simvastatin during a 4-year period from 2006 to 2010. Study results revealed a non-significant difference (P=0.081) between the percentage of subjects on simvastatin with HE (22%) and those not taking simvastatin with HE (39%; Figure 2).

![Figure 2: Percentage of subjects with cirrhosis on simvastatin with HE and those not taking simvastin with HE.](image)

The results of the univariable analysis revealed that the development of HE was significantly associated with higher Model for End-Stage Liver Disease and Child-Turcotte-Pugh (CTP) scores, the presence of hepatitis C, and low levels of sodium (< 135 mEq/ml). The results of the multivariable logistic regression analysis showed that the use of simvastatin was not significantly associated with HE, but that subjects with CTP scores of class B (7-10) or class C (11-15) and sodium levels < 135 mEq/ml were 5.8 and 4 times, respectively, more likely to have HE than those who had CTP scores of class A (5-6) and sodium levels > 135 mEq/ml (Table 3).

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Simvastatin use</td>
<td>0.79 (0.26, 2.3)</td>
<td>.67</td>
</tr>
<tr>
<td>CTP B/C vs A</td>
<td>5.8 (1.9, 17.9)</td>
<td>.002</td>
</tr>
<tr>
<td>Na &lt;135 vs 135-145 mEq/ml</td>
<td>3.9 (1.3, 11.3)</td>
<td>.01</td>
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Table 3. Odds ratios and significance levels of several factors associated with HE as determined by multivariable logistic regression analysis in 91 patients with cirrhosis. A = Child-Turcotte-Pugh score, class A (5–6); B = Child-Turcotte-Pugh score, class B (7–10); C = Child-Turcotte-Pugh score, class C (11-15); CI = confidence interval; CTP = Child-Turcotte-Pugh score; Na = sodium; OR = odds ratio.

The study authors concluded that patients with cirrhosis on simvastatin had a decreased prevalence of HE compared with those not on simvastatin, but noted that simvastatin did not...
appear to significantly reduce rates of HE in cirrhotic patients. They suggested that larger studies would be necessary.

**Summary**

HE is a complex neuropsychiatric syndrome that complicates up to 1 in 4 presentations of ALF. The clinical manifestations of the low-grade cerebral edema associated with altered neuron-astrocyte crosstalk exacerbated by hyperammonemia and oxidative stress are broad, debilitating, and life-threatening. The often observed hyperammonemia characteristic of HE is a result of gut-liver axis dysregulation in cirrhosis which allows ammonia to bypass the liver and enter the systemic circulation. Despite a great deal of research, however, the exact relationship between ammonia and HE remains to be elucidated. Of the American College of Gastroenterology 2013 poster presentations summarized here, two pertained to the burden of HE, one in the greater context of cirrhosis burden in inpatients and the other in those with RLS or small intestinal bacterial overgrowth. Two additional poster presentations were treatment-focused: one described the success rate and optimal procedure for TIPS revisions in those with HE; the other demonstrated that patients with cirrhosis on simvastatin had a decreased prevalence of HE compared with those not on simvastatin, but that simvastatin did not appear to significantly reduce rates of HE in cirrhotic patients.
References


Posttest

If you wish to receive acknowledgement of participation for this activity, please complete this posttest, evaluation form, and request for credit (pages 6-9) and fax to 973-939-8533.

Required with 70% Passing. Must get 4 out of 5 answers correct.

1. What percentage of patients with liver cirrhosis are estimated to suffer with a form of HE referred to as minimal hepatic encephalopathy?
   a. Between 20% and 40%
   b. Between 40% and 60%
   c. Between 60% and 80%
   d. Between 80% and 100%

2. In the study by Sethi et al, what percentage of discharges in 2010 were attributable to HE?
   a. 36.8%
   b. 46.8%
   c. 56.8%
   d. 66.8%

3. In the study by Basu et al, which group of patients had the largest number and percentage with either RLS or SIBO?
   a. Decompensated cirrhotics
   b. Patients with chronic liver disease without cirrhosis
   c. Healthy controls
   d. None of the above

4. The results of the study by Olaywi et al revealed that:
   a. 9 TIPS revisions using a variety of techniques were performed on the 11 patients and that 6 of the 9 revisions were considered to have been successful based on improved hepatopedal flow and improvement in HE
   b. 11 TIPS revisions using a variety of techniques were performed on the 9 patients and that 9 of the 11 revisions were considered to have been successful based on improved hepatopedal flow and improvement in HE
   c. 11 TIPS revisions using a variety of techniques were performed on the 9 patients and that 6 of the 11 revisions were considered to have been successful based on improved hepatopedal flow and improvement in HE
   d. 9 TIPS revisions using a variety of techniques were performed on the 11 patients and that 9 of the 9 revisions were considered to have been successful based on improved hepatopedal flow and improvement in HE

5. The results of the study by Wakim-Fleming et al demonstrated:
   a. significant difference (P=.041) between the percentage of subjects on simvastatin with HE (22%) and those not taking simvastatin with HE (39%)
   b. non-significant difference (P=.081) between the percentage of subjects on simvastatin with HE (22%) and those not taking simvastatin with HE (39%)
   c. non-significant difference (P=.081) between the percentage of subjects on simvastatin with HE (39%) and those not taking simvastatin with HE (22%)
   d. significant difference (P=.041) between the percentage of subjects on simvastatin with HE (39%) and those not taking simvastatin with HE (22%)
Purdue University College of Pharmacy respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form.

**How well did this activity meet the following learning objectives?**

<table>
<thead>
<tr>
<th>This learning objective did (or will) increase/improve my:</th>
<th>High Impact</th>
<th>Moderate Impact</th>
<th>No Impact</th>
<th>Not Applicable</th>
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<tbody>
<tr>
<td>Knowledge</td>
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<td>Patient Outcomes</td>
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- Recognize the central role of aberrant nitrogen metabolism in the pathogenesis of hepatic encephalopathy
- Assess the results of selected studies relating to the burden and treatment of hepatic encephalopathy presented at the American College of Gastroenterology 2013 Annual Scientific Meeting and Postgraduate Course

**Impact of the Activity**

- Please indicate which of the following American Board of Medical Specialties/Institute of Medicine core competencies were addressed by this educational activity (select all that apply):
  - Patient care or patient-centered care
  - Interdisciplinary teams
  - Practice-based learning and improvement
  - Professionalism
  - Interpersonal and communication skills
  - Quality improvement
  - Employ evidence-based practice
  - Medical knowledge
  - System-based practice
  - Utilize informatics
  - None of the above

- The content of this activity matched my current (or potential) scope of practice.
  - No
  - Yes, please explain

- Was this activity scientifically sound and free of commercial bias* or influence?
  - Yes
  - No, please explain

*Commercial bias is defined as a personal judgment in favor of a specific product or service of a commercial interest.

**Impact of the Activity**

- The educational activity has enhanced my professional effectiveness in treating patients

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<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
<th>Not Applicable</th>
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- The educational activity will result in a change in my practice behavior

This material was supported by an educational grant from Salix Pharmaceuticals, Inc.
Evaluation

• How will you change your practice as a result of participating in this activity (select all that apply)?

  ❑ Create/revise protocols, policies, and/or procedures
  ❑ Change the management and/or treatment of my patients
  ❑ This activity validated my current practice
  ❑ I will not make any changes to my practice
  ❑ Other, please specify: ________________________________

• What new information did you learn during this activity?

  ______________________________________________________
  ______________________________________________________

• Please indicate any barriers you perceive in implementing these changes.

  ❑ Lack of experience
  ❑ Lack of resources (equipment)
  ❑ Lack of time to assess/counsel patients
  ❑ Lack of consensus of professional guidelines
  ❑ Lack of opportunity (patients)
  ❑ Lack of administrative support
  ❑ Reimbursement/insurance issues
  ❑ Patient compliance issues
  ❑ No barriers
  ❑ Cost
  ❑ Other ________________________________

• If you indicated any barriers, how will you address these barriers in order to implement changes in your knowledge, competency, performance, and/or patients’ outcomes?

  ______________________________________________________
  ______________________________________________________
  ______________________________________________________

• Comments to help improve this activity?

  ______________________________________________________
  ______________________________________________________
  ______________________________________________________

• Recommendations for future CME/CPE topics.

  ______________________________________________________
  ______________________________________________________
  ______________________________________________________

To assist with future planning, please attest to time spent on activity:

I spent _____ hours on this program
Evaluation

If you wish to receive acknowledgement of participation for this activity, please complete this posttest, evaluation form, and request for credit (pages 6-9) and fax to 973-939-8533.

Please do not use abbreviations. We need current and complete information to assure delivery of participation acknowledgement.

Degree (please mark appropriate box and circle appropriate degree)

☐ MD/DO ☐ PharmD/RPh ☐ NP/PA ☐ RN ☐ Other ______________________

Full Name (please print clearly)

Last Name: ____________________________________________

First Name: __________________________________________

Middle Initial: ________________________________________

Street Address: ________________________________________

City: __________________________________________ State or Province: __________________________________

Postal Code: ___________________________

Phone: __________________________ Ext: __________________________ Fax: __________________________

Specialty: ______________________________________

E-mail Address: ______________________________________

Date Completed: __________________________

Attestation to time spent on activity is required

☐ I participated in the entire activity and claim 0.75 AMA PRA Category 1 Credit(s)™. ☐ I participated in only part of the activity and claim ________ credits

☐ I do not wish to claim credits